

Dissolution Performance Improvement of Fenofibrate through Secondary Solid Dispersion Using PEG6000 and Croscarmellose Sodium Combination

A Project Submitted

By

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Inspiring Excellence

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Dedicated to my parents, who sacrificed their every desire since my birth and inspire me in every step of my life and to my beloved friend Farhana Jafrin Onee

Certification Statement

This is to certify that this project titled “Dissolution Performance Improvement of Fenofibrate through Secondary Solid Dispersion Using PEG6000 and Croscarmellose Sodium Combination ” submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy, BRAC University constitutes my own work under the supervision of Mrs. Shahana Sharmin, Senior Lecturer, Department of Pharmacy, BRAC University and that proper credit has been given where I have used the language, ideas or writings of another.

Signed,

Countersigned by the supervisor

Acknowledgment

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Abstract

The potential of solid dispersion based formulation using the combination of PEG6000 and croscarmellose sodium as drug carrier to enhance the dissolution performance and oral bioavailability of Fenofibrate, a poorly water soluble drug was investigated. Fenofibrate is a hydrophobic drug in fibrate class of drug which is mainly used in patients at risk of cardiovascular disease in the treatment of hypercholesterolemia and hypertriglyceridemia. Solid dispersions with different drug-to-carrier ratios were prepared by the physical mixture method and solvent method and characterized by dissolution testing within 30minutes. In vitro drug release were performed using US pharmacopeia type II apparatus (paddle-method) in 1000ml distilled water containing 0.75% w/v sodium lauryl sulfate at 75rpm for 30minutes. UV visible spectrophotometric method was selected for dissolution performance investigation at λ_{\max} 290 nm. In physical mixture method F5 (32.5%) and F11 (83%) and in solvent method F6 (39%) and F11 (38.5%) have showed good percentage of drug release.

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List of Acronyms:

GI Tract = Gastrointestinal Tract

BCS = Biopharmaceutical Classification System

FDA = Food and Drug Administration

IR = Immediate Release

SLS = Sodium Lauryl Sulfate

NSAIDS = Non-Steroidal Anti-Inflammatory Drugs

PVP = Polyvinylpyrrolidone

HPMC = Hydroxy Propyl Methyl Cellulose

NCE = New Chemical Entities

PEGs = Polyethylene Glycols

MW = Molecular Weight

MC = Methyl Cellulose

HPC – Hydroxy Propyl Cellulose

VLDL = Very Low Density Lipoprotein

TGs = Triglycerides

PPAR- α = Peroxisome Proliferation Activated Receptor α Gene

LDL = Low Density Lipoprotein

USP = United States of Pharmacopoeia

BP = British Pharmacopoeia

PD = Pure Drug

Chapter 1:

Introduction

1.1 Introduction

The release of drug substance from the delivery system is depended upon drug absorption from solid oral dosage form, the dissolution of drugs under the physiological conditions and the drug permeability across the GI tract (Tiwari, Tiwari, Srivastava, & Rai, 2009). Dissolution is the rate limiting step in case of absorption for poorly water soluble drugs. So increase solubility can increase drug absorption and in result, drug bioavailability. Solid dispersion technique is a popular method to improve the dissolution and consequently the bioavailability of poorly water soluble drugs (Singh, Baghel, & Yadav, 2011).

1.2 Solubility

Solubility is an important feature of a liquid, solid or vaporous solute that dissolve in a liquid, solid or vaporous solvent to obtain a homogeneous solution of the solute in the solvent. The solubility of a solute depends in the solvent used, temperature and pressure. Saturation concentration measures the level of solubility of a substance in a particular solvent in which addition of more solute does not improve the concentration of that solute in the solution (Lachman, Lieberman, & Kanig, 1986).

The unadulterated solvent is normally a liquid or a mixture of two liquids, solid solution and even a gas. Solubility measurement widely ranges from infinitely soluble (completely miscible- e.g. ethanol in water) to poorly soluble (e.g. silver chloride in water). For poorly or very poorly soluble compounds are termed as insoluble compounds in a specific solvent. (Clugston & Fleming, 2000).

Sometimes solubility is mistaken with the capacity to melt or dissolve a substance in the dissolution process and for the chemical reaction. For instant, zinc chemically reacts with hydrochloric acid to form zinc chloride yet zinc is insoluble in hydrochloric acid. In addition, solubility does not depend on the molecular size of components in the formulation (Martin, 2011).

Solubility broadly expresses in different ways like as a concentration, either by mass, molarity, molality, mole fraction etc. the solubility of the solute in this way can be defined as the maximum equilibrium amount of solute to dissolve per amount of solvent (Aulton, 2007) . The major disadvantage in this way is it's dependability upon the different species present in the solvent.

1.3 Dissolution

Poorly water soluble drugs show very negligible availability which next result in their low dissolution performance. Consequently, it delays the absorption from the gastrointestinal tract. Solubility property of a drug is really an important factor.

Dissolution performance relies on the solubility and permeability of the oral dosage form. If the drug solubility in water is less than 10mg/ml, dissolution is considered as rate limiting step for the process of drug absorption.

Two important points are involved in drug dissolution. One is the transportation of drug within the dissolution medium and second is drug release from the dosage form.

The factors affecting dissolution are-

- Physical and chemical properties of drug(e.g. drug's solubility. drug's particle size, drug's molecular structure)
- Characteristics of formulation (e.g. excipients, coating substance)
- Techniques for dissolution (e.g. types of apparatus, volume, viscosity and p^H of the dissolution medium etc), (Abdou, 1989)

From the Noyesh-whitney equation the hints to improve dissolution rate of drugs specially poorly soluble drugs in water can be obtained.

$$dc/dt = AD(C_s - C)/h$$

Where-

dc/dt – The rate of dissolution

A- The available surface area for dissolution

D- Compound's dissolution coefficient

C_s – Compound's solubility in the dissolution medium

C – The concentration of drug in the medium at time t and

h- The thickness of the diffusion boundary layer which is adjacent with the surface of the dissolving compound

So to increase dissolution performance of the poor water soluble drugs following approach can be used according to the Noyes- Whitney equation-

- increasing the surface area that is available for dissolution

- decreasing the particle size of the insoluble drug

- to optimize the wetting features of compound surface

- decreasing the boundary layer thickness

- ensuring sink condition for dissolution

- administration of drugs in the feed state

- to improve apparent solubility of drug under physiological relevant conditions

Among all these possibilities maintaining the sink condition depends on the permeability of the gastrointestinal mucosa of the compounds, and on the composition as well as volume of the luminal fluids (Singh, Baghel, & Yadav, 2011).

1.4 Biopharmaceuticals Classification System

Taking into accounts the aqueous solubility, dissolution characteristics of the drug and intestinal permeability drug substances are classified into a logical classification that can connect both in vitro disintegration and in vivo bioavailability of the drugs. This classification is termed as Biopharmaceutics classification system (BCS) (Wagh & Patel, 2010).

In BCS point of view, the solubility class obtains by calculating the sufficient volume of aqueous medium that is needed to dissolve the highest anticipated dose strength. When the highest strength of a drug is soluble in 250ml or less aqueous medium over the p^H range 1 to 8, the drug is called a highly soluble drug. When a test drug has an extent of absorption >90% from the intestinal mucosa in humans, the drug is considered as highly permeable drugs.

Table 1.1: The Biopharmaceutical classification system

BCS Class	Solubility	permeability	Absorption pattern	Examples of drugs
Class I	High	high	Well	
Class II	Low	High	Well	Metoprolol, propranolol
Class III	High	Low	Various	Danazol, nifedipine
Class IV	Low	Low	poor	Taxol, furosemide

From FDA Guidance for industry (2000) and Amidon et al (1995)

Drug dissolves very fast and drug absorption is good in class I drugs. There is no bioavailability problem usually in this class for IR drug products. Dissolution is a rate limiting step for class II drugs and bioavailability is generally controlled by the drug dosage form as well as release rate of the drug substance. Drug is permeability limited in class III drugs and bioavailability may not be completed if drug is not released from the dosage form and dissolved in the absorption window. Finally, both the dissolution and permeability are limited steps and an alternative route of administration is needed for class IV drugs (Shargel, Wu-Pong, & Yu, 2012).

Solid dispersion technique is used to increase the solubility and dissolution performance of drugs by using carriers with the target drug. In this case, BCS II drugs are the suitable candidates for solid dispersion technique as dissolution is the rate limiting step for the absorption of drugs in this class and solid dispersion techniques can show promising improvement of the dissolution performance (Singh, Baghel, & Yadav, 2011).

1.5 Definition of Solid Dispersion

Sekiguchi and Obi in 1961 first proposed the utilization of solid dispersion for increasing the dissolution performance and oral bioavailability of poorly water soluble drugs. They proposed a solid dispersion formulation as a eutectic mixture where the poorly water soluble drugs are dispersed in a physiologically inert and easily water soluble carriers.

Next, Chiou and Riegelman in 1971 termed solid dispersion as “the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method”.

Mayersohn and Gibaldi in 1966 called solid dispersion as “Solid State”.

Corrigan defined solid dispersion as “Product formed by converting a fluid drug-carrier combination to the solid state”.

In current review works Dhirendra et al defined solid dispersion as “a group of solid products consisting of at least two different components, generally a hydrophilic matrix and hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles” (Saffoon, Uddin, Huda, & Bishwajit, 2011).

Some drugs whose solubility performance is enhanced by solid dispersion are- Mifepristone, Dihydroartemisinin, Furosemide, Piroxicam and Others (Ingle, Gaikwad, Bankar, & Pawar, 2011).

1.6 Advantages of solid dispersion

The common advantages of solid dispersion are-

1. Particles with reduced particle size and increased dissolution rate:

From the Noyes –whitney equation it is clear that increasing the surface area is one way to increase the dissolution of the poor water soluble drugs and this can be obtained through reducing particle size. For reducing particle size many common methods are used like micronization, recrystallization, and freeze drying and spray drying. For many years micronization is used to reduce the particle size in the pharmaceutical industries but the main disadvantages are aggregation, agglomeration and poor wettability of the fine particles. This leads to have poor dissolution performance. On the other hand, in solid dispersion the particle size of the drug is reduced to the minimum level to prevent aggregation and agglomeration. Additionally, the solubilizing and wettability properties of the carriers contribute to increase the dissolution rate.

2. Particles with improved Wettability:

The enhancement of solubility of poor water soluble drugs is due to the improved wettability of the particles and carriers used in the solid dispersion contribute this property. Moreover, addition of surface active agents in the third generation solid dispersion with both drug and polymeric carriers greatly enhance the dissolution of the drug particles.

3. Particles with higher porosity:

Normally the increased porosity can lead to increase drug release profile and the carriers used in the solid dispersion usually contribute the porosity of the particles in the formulation.

4. Drugs in Amorphous state:

Amorphous state of crystalline drugs which are poorly water soluble has greater water solubility due to no energy requirement to break up the crystalline lattice in the dissolution process. Second and third generation solid dispersions are in the amorphous state and thus enhance the dissolution performance (Kumari, Chandel, & Kapoor, 2013).

1.7 Applications of Solid Dispersion

Some of the applications of solid dispersion are given below-

- In case of lung transplant patients, it helps to improve immunosuppressive therapy through formulation of dry powder solid dispersion for inhalation. This formulation can avoid problems associated with the use of local anesthesia and irritating solvents.
- Solid dispersion formulations accelerate the onset of action of NSAIDS when they are needed crucially for acute pain and inflammation.
- To improve patient comfort and compliance the standard injections of anti cancer drugs can be substituted with their oral dosage solid dispersion form (Kumari, Chandel, & Kapoor, 2013).

1.8 Disadvantages of Solid Dispersion

2. Problems with dosage form Formulation:

a. Poor flow and compressibility-

In sieving and pulverization process, solid dispersion shows complexity. In addition it shows compressibility and stability problems.

To avoid these problems drug granulation follows in-situ granulation method. At first the excipients are pre-heated and rotated by using water jacket blender at 70°C. Next, the drug and carrier mixture is melted at 100°C and is added in the moving power of excipients. After that, granules are passed through a 20-mesh sieve and harden at 25°C. Finally, magnesium stearate (1%) is mixed with the granules and compressed to form tablets. However, wet granulation process cannot use here due to the possibility of disruption of its physical structure.

b. Sticking of granules of solid dispersion to Die and Punches:

The formulations of solid dispersion usually stick to the die and punches. For that, a grease proof paper is placed between the metal surface of the die and punches and the granules to avoid their direct contact.

3. Problems with manufacturing:

a. Risk of moisture during cooling process of the solid dispersion:

In the condensation process during evaporation moisture can be trapped in the solid dispersion. A continuous cooling process is done on the surface moving belt or rotating to avoid this problem.

b. Reproducibility of the physical and chemical properties:

Investigators observe that the manufacturing conditions like rate of heating, the temperature, and rate of cooling and cooling methods, pulverization methods, and particle size influence the physical and chemical properties of solid dispersion.

c. Stability problems:

In hot melt method, a certain fraction of drug sometimes remains dispersed in carrier molecularly. That result in the separation of amorphous and crystalline phase.

To overcome such problems some common carriers like PVP, HPMC etc are used. These carriers form kinetic barrier to nucleation and the rate of efficiency of the barrier is directly proportional to the concentration of the polymer and is independent of the physical and chemical properties of that polymer. (Ingle, Gaikwad, Bankar, & Pawar, 2011) (Craig, 2002).

1.9 Advantages of Solid Dispersions over the Other Strategies

The popular strategies to improve the dissolution and bioavailability of poor water soluble drugs can be divided into two categories, they are-

- Chemical Approaches
- Formulation Approaches

Chemical Approaches:

In this approaches the bioavailability of poorly water soluble drugs are increased by using one of the following ways-

- Salt Formation
- Introducing a polar group in the Structure
- Introducing an ionized group. In these ways the active target site of the drugs is kept unchanged and resulting in the formation of pro-drugs.

However, Chemical approaches have such limitations like-

- Formation of pro-drug is difficult task
- Salt formation can only be used for weakly acidic or basic drugs but not for the neutral
- Salt formation can hamper the bioavailability of drugs *in vivo* due to the formation of acidic or basic form
- In case of NCE, sponsoring company has to perform clinical trials for chemical approaches
- On the other hand, solid dispersions have no such problems. They are easy to produce and more applicable. In addition, the formulation of drugs in solid dispersion techniques gives option to choose methods among various methods and excipients option. Hence, the process provides flexibility to formulate oral dosages form of poor water soluble drugs (Singh, Baghel, & Yadav, 2011).

Formulation Approaches:

Formulation approaches to improve the aqueous solubility of poor water soluble drugs are-

- Particle Size Reduction
- Solubilization
- Solid Dispersion.

Between the solubilization and solid dispersion, solid dispersion are more preferable to most of the patients since it provides the solid oral dosages form then the products of solubilization.

The particle size reduction is most common way to improve the bioavailability of poor water soluble drugs on the basis of increase surface area of the drugs, but it also has certain disadvantages which limit its use to use as a convenient method to improve aqueous solubility. The disadvantages are-

- The limit of the milling or micronization process to reduce particle size is around 2-5mm which does not frequently increase the bioavailability and the drug release in the small intestine.
- They have poor mechanical properties such as low flow properties and high adhesion capacity.
- The fine particles of the drugs are difficult to handle.
- Micronizing of drugs can lead to formation of agglomerate of particles which gives poor wettability of drugs.

The water soluble carrier in solid dispersion reduced all the above problems and increase dissolution. The drugs need not to be micronized in solid dispersions. Here the fraction of drug molecularly disperse in the matrix of carrier and in exposure of aqueous media the carrier dissolve where drug releases as fine colloidal. This gives greater dissolution rate as a result of sufficient surface area enhancement. Moreover, one portion of drug dissolves and saturates the gastrointestinal fluid and rest of the drugs precipitates as fine colloidal particles or oily globules of submicron size (Singh, Baghel, & Yadav, 2011).

1.10 Factors that Influence the Drug Release from the Solid Dispersion

Nature Of carriers:

Drug release of poorly water soluble drug from the formulation depends on the nature of the carriers used in the formulation. The nature of carriers can be either hydrophilic or hydrophobic. So, incorporation of drug in hydrophobic or slightly water soluble carrier result in retardation of drug release from the matrix and incorporation of drug in hydrophilic or water soluble carriers result in acceleration of drug release.

Drug Carrier Ratio:

The dissolution rate of drug release increases with the increase proportion of drug carrier but it is up to certain limit of the ratio. Beyond the certain limit the rate of the drug dissolution decreases.

Method of Preparation:

Generally solid dispersion prepared by melting method shows greater effect and faster dissolution rate the solvent method and co-grinding method. However, among all the methods a particular method can show greater effectiveness for a particular solid dispersion formulation.

Cooling condition:

The cooling condition is a important factor specially for the solid dispersion prepared by melting method. The rate of cooling whether faster or slower affects the rate of dissolution.

Synergistic Effect of Two Carriers Used:

If two carriers are used in the solid dispersion technique, their synergistic effect is then considered as an important factor. The different properties of two carriers can attribute to increase the dissolution performance of the poorly water soluble drugs (Bhusnure, Kazi, Gholve, Ansari, & Kazi, 2014).

1.11 Classification of Solid Dispersion

Solid dispersion is classified on the basis of two criteria-

- On the basis of carrier used
- On the basis of solid state structure in the solid state (Bhusnure, Kazi, Gholve, Ansari, & Kazi, 2014)
- On the basis of carrier used solid dispersion is classified into three types. They are briefly described below-

I. First generation solid dispersion:

In 1961, Sekiguchi and Obi developed first generation solid dispersion. First generation solid dispersion is prepared by crystalline carriers for instance urea, sugar. The preparation of eutectic mixture that was prepared by Sekiguchi and Obi showed better drug release which resulted in increased bioavailability than the conventional formulations of the same drug. The main reasons of this better drug release are small particle size and the better wettability (Singh, Baghel, & Yadav, 2011).

The major disadvantage of this type is it leads to the formation of crystalline solid dispersion that is thermodynamically more stable than the amorphous ones results in slower drug release from the dosage form (Kumari, Chandel, & Kapoor, 2013).

II. Second generation solid dispersion:

A second generation solid dispersion appeared in the late sixties to overcome the problems associated with the first generation solid dispersion. Here polymers are used instead of crystalline carriers.

This type originates a homogenous molecular interaction between drug and polymeric carriers because they are totally miscible, soluble and possesses higher interaction energy between the drug and the carriers. It also reduce particle size and gives better wettability to increase the bioavailability of the poorly water soluble drugs but works greater than the first generation solid dispersion (Singh, Baghel, & Yadav, 2011).

The different kinds of polymers used in the second generation are-

- Fully synthetic polymers-
E.g. polyvinylpyrrolidone (povidone), polyethylene glycols, polymethacrylates.
- Natural product based polymers (cellulose derivatives, starch derivatives)-
E.g. hydroxypropylmethylcellulose, ethylcellulose, hydroxypropylcellulose, cyclodextrins (Bhusnure, Kazi, Gholve, Ansari, & Kazi, 2014).

III. Third generation solid dispersion:

The third generation solid dispersion appears to solve the problems with first and second generation. Second generation solid dispersion has some common problems like recrystallization, chemical and physical instability etc. fortunately addition of surfactants with the second generation carriers can solve almost all the problems associated with second generation solid dispersion. So, adding surface active agent with the polymeric carriers is referred to as third generation solid dispersion. In third generation solid dispersion, the formulation can be stabilized for at least sixteen months. It also helps the formulation containing polymeric carriers to prevent recrystallization and precipitation which can be occurred from the agglomeration of much larger hydrophobic particles (Singh, Baghel, & Yadav, 2011).

The common surfactants used in the third generation solid dispersion are inulin, inutec SP1, compritol 888 ATO, gelucire 44/14 and poloxamer 407 (Bhusnure, Kazi, Gholve, Ansari, & Kazi, 2014).

- On the basis of solid state structure, solid dispersion is classified into following ways-

A. Drug and polymer exhibiting immiscibility in the fluid state:

The immiscible mixtures of drug and polymer in their fluid state are grouped in this class. In addition, the mixture of drug and polymer normally do not exhibit miscibility on the solidification of the fluid state and phase separation can be occurred. They may enhance the dissolution performance through following ways-

-modifying the morphology of drug and/or polymer because of physical transformation.

- intimate drug/polymer mixture

-enhancing surface area

However, the rate of solidification of mixture and the rate of crystallization process of drug and/or polymer bias the formation of crystalline solid dispersion and amorphous solid dispersion.

B. Drug and polymer exhibiting miscibility in the fluid state:

The miscible mixtures of drug and polymers in their fluid state may or may not show miscibility and phase separation in their solidification process. Additionally, this state influences the structure of solid dispersions.

C. Eutectic Mixtures:

In 1961 Sekiguchi and Obi described eutectic mixture as solid dispersion. When drug and polymer are miscible in their molten state but on cooling they form two separate components with negligible miscibility is referred to as eutectic mixture. Generally, the melting point of the eutectic mixture is lower than the components of the mixture. Here the mechanism is to increase the surface area of the drug to enhance the bioavailability.

D. Crystalline solid dispersion:

In the crystalline solid dispersion, the rate of drug crystallization from the drug/polymer miscible mixture is greater than the rate of the solidification of the drug/polymer in their fluid state.

E. Amorphous solid dispersion:

Amorphous solid dispersion can be formed if the drug crystallization is not allowed by the cooling rate of drug/polymer cooling fluid mixture. This state can also be referred as “solidified-liquid” state. Still, the amorphous solid dispersion has potential to form a more stable and less soluble crystalline formulations.

F. Solid solution:

When drug/polymer mixture is miscible in both fluid and solid state, it is called solid solution. Generally there are two types of solid solution-

1. Amorphous solid solution
2. Crystalline solid solution

1. Amorphous solid solution:

Amorphous solid solutions are those where the drugs are molecularly dispersed in the carrier matrix and miscible in both fluid and solid state. This type of solid dispersion is effective as it increases the surface area in greater rate and enhances the dissolution performance. Moreover, it enhances physical stability of the formulation through preventing crystallization by minimizing molecular mobility.

2. Crystalline solid solution :

When a crystalline drug is trapped in crystalline carrier with miscibility in both fluid and solid state then the solid dispersion is termed as crystalline solid solution.

Again on the basis of miscibility solid solution is divided into two types-

1. Continuous solid solution
2. Discontinuous solid solution

1. Continuous solid solution:

The two components are miscible in their solid state in all proportion in case of continuous solid dispersion.

2. Discontinuous solid solution:

In discontinuous solid dispersion, the two components are immiscible in their intermediate composition but miscible at extremes of composition.

Furthermore, on the basis of the size of the molecule of the two components, solid solution is divided into two types. They are-

1. Substitutional solid solution
2. Interstitial solid solution

1. Substitutional solid solution:

In the crystal lattice the solute molecules substitute for the solvent molecule to obtain substitutional solid solution and the molecular size of the two components should not exceed 15%.

2. Interstitial solid solution:

When the solute molecule occupies the interstitial space in the solvent lattice, interstitial solid solution can be obtained. Here, the solute is referred to as the guest and the solvent is referred to as the host. For the interstitial solid solution the ideal molecular diameter of the solute should be less than 0.59 times the molecular diameter of the solvent. In addition, the volume of the solute molecules should be less than 20% of the volume of the solvent molecules (Bhusnure, Kazi, Gholve, Ansari, & Kazi, 2014).

1.12 Methods of Solid Dispersion

There is numerous method of solid dispersion. Among them the most common methods are described briefly in below-

1. Kneading Technique

In this method, at first carrier and drugs are weighted separately. Then carriers are wetted with water and turn into paste. Next, drugs are added to the paste and kneaded for a particular time. Lastly, the mixture is dried and passes through sieve.

2. Solvent evaporation method

In solvent evaporation method drugs and carrier are weighted and dissolve in a suitable organic solvent. After that the solvent is evaporated. Finally, the solid mass is grounded, sieved and dried.

3. Co-precipitation method

Co-precipitation method involves both water and solvent. Firstly, drug is dissolve in a suitable organic solvent and carrier is dissolve in water. Next, the aqueous solution of carrier is added to the drug solution. Then, the solvent is evaporated through heat and pulverized by using mortar and pestle. Finally, the mixture is dried and sieved.

4. Melting method

Drugs and carrier are weighted perfectly. Next, the drug and carrier are mixed homogenously by the help of mortar and pestle. Then the whole mixture is melted through heating at or above the melting point of all the components to get a homogenous dispersion. After that, the mixture is cooled, pulverized in mortar and pestle, sieved and dried.

5. Co-grinding method

This is one of the simple methods of solid dispersion. In this method the physical mixture of drug and carrier is obtained through mixing in blender for some time at a particular speed. Finally, the mixture is pulverized, sieved and stored in dry place at room temperature.

6. Gel entrapment technique

Here carrier is dissolved in suitable organic solvent and made it into transparent and clear gel. Then the drug is dissolved in the gel by sonication for few minutes. Next, the solvent is evaporated under vacuum condition. Finally the solid dispersion is reduced in size by mortar and sieved.

7. Spray-Drying Method

Spray dry method is a new approach. In this method, drug is dissolve in suitable organic solvent and carrier is dissolved in water. Afterwards, solution is mixed through sonication or other suitable methods to get a clear solution. In the final step the solution is spray dried using spray drier.

8. Lyophilization Technique

This is a costly procedure. Lyophilization technique is also regarded as an alternative method of solvent evaporation. It is a molecular mixing technique where both drug and carrier are co-dissolve in a common solvent. Finally the solution is frozen and sublimed to achieve a lyophilized molecular dispersion.

9. Electrospinning Method

In future this technique can be used in the preparation of solid dispersion. The technique is the combination of the dispersion technology with the nanotechnology. The stream of liquid of solid dispersion solution is given a potential between 5 and 30 kV. As a result fibers of submicron diameters are produced. The fibers can be collected on a screen after the evaporation of the solvent. Since the technique is simplest and cheapest for producing nanofibers and controlling the release of biomedicine, the technique has great potential.

10. Dropping method solution

In 1997, Ulrich developed the dropping method. The method is said to facilitate the crystallization process of various chemicals and produces round shape particle in solid dispersions. At first, physical mixture of drug-carrier is melted at or above the melting point of the components through heating. Next the melted solid dispersion is pipette and is dropped on to a plate. Therefore, it produces round particles upon solidification. The use of carriers that solidifies at room temperature facilitates the process. As it does not involve any use of solvent it can overcome problems associated with solvent evaporation method. However, the size and shape of the particles can be influenced by the pipette size, temperature require to solidify and viscosity of the melted mixture.

11. Direct Capsule Filling

Liquid melt of solid dispersions can directly fill in to the hard gelatin capsule. As a result it can avoid the problems associated with grinding procedure like changes in the crystallinity of the drug. It can also avoid cross contamination and operator exposure in the dust-full environment. In addition, it facilitates better fill weight and content uniformity (Singh, Baghel, & Yadav, 2011) (Kumari, Chandel, & Kapoor, 2013) (Saffoon, Uddin, Huda, & Bishwajit, 2011).

12. Physical Mixture Method

It is one of the simple methods in solid dispersion technique but not so effective. However, homogenous mixture of drugs and carriers can be obtained from drugs and carriers are weighed and then mixing them in a mortar and pestle by triturating. The resulted physical mixtures are passed through 44-mesh sieve (generally) and are stored in desiccators until used for further (Bonthagarala, Nama, Nuthakki, Kiran, & Pasumsrthi, 2014).

1.13 Criteria for the selection of carriers

In solid dispersion the performance of the dissolution is improved due to the properties of the carriers. Selection of a suitable carrier or mixture of carriers for a particular water insoluble drug follows some common criteria. They are-

- They should be water soluble and also readily soluble in gastrointestinal fluids
- They should be physiologically inert
- The melting point of the formulation with drug and carrier should be less than of the drug
- The carrier should have thermal stability at melting temperature
- They should have low vapor pressure
- The carriers should have high molecular weight
- They must be non-toxic (Tiwari, Tiwari, Srivastava, & Rai, 2009)

1.14 Polymers used in the Solid Dispersion

Sugars:

Sugars are highly water soluble but due to the toxicity issues, they are not widely used in the solid dispersion preparation.

Sugars that are commonly used in the solid dispersion formulation are dextrose, sucrose, lactose, sorbital, maltose, mannitol, galactose.

Acids:

Several researches found out that the rate of drug release can be increased twenty times with the use of these organic acids. Moreover, they can also increase stability of the formulation like citric acid shows improved stability in inhalation formulation of spray-dried insulin powder.

E.g. citric acids, succinic acids, tartaric acids etc

Polymeric materials:

- a. PEGs are the polymers of ethylene oxide and have MW in the range $200 \pm 3, 00,000$. Generally their water solubility is good but the solubility can decrease with MW. The major advantages of PEGs are they are soluble in many organic solvent and their melting point (m.p.) remains under 65°C . Production of product with sticky consistency is the main disadvantage of lower MW PEGs.

- b. Polyvinyl pyrrolidone (PVP)-

PVP is the polymerization of vinylpyrrolidone and their MW ranges from 2500 to 3,00,000. The advantageous points of PVP are their good solubility in many organic solvents, good solubility in the water and can improve the wettability of the dispersed substances. Additionally the chain length is an important factor for increasing the water solubility of poor water soluble drugs. The aqueous solubility of the PVPs decreases and they become less viscous with the increased chain length.

- c. Cellulose derivatives-

Naturally occurring polysaccharides are known as cellulose and they have higher molecular weight unbranched chains which forms through joining the saccharide units linking by β -1, 4-glycoside bonds.

Common cellulose derivatives are MC, HPC, HPMC, pectin

Emulsifiers:

Through two mechanisms namely solubilization of the drugs and improvement of wettability emulsifiers increase the dissolution performance that results in increase aqueous solubility of poor water soluble drugs. However for exhibiting toxicity they are used with the other carriers in the solid dispersion preparations.

E.g. poloxomers, gelucire 44/14 and other grades of gelucire etc. Bile salts and their derivatives are natural emulsifiers.

Surfactants-

Surfactants are used in the third generation solid dispersion to improve the surface area of the particles to enhance the aqueous solubility of poorly water soluble drugs in greater way.

E.g. poloxamers, Tweens (polyethoxylated sorbitan esters), Spans (sorbitan esters), polyoxethylene stearates etc.

Miscellaneous:

Other carriers are urea (the end product of human protein metabolism), urethanes (a class of synthetic elastomers), and polyurethane (a polymer containing a chain of organic units joined by urethane or carbamate links) (Kumari, Chandel, & Kapoor, 2013).

1.15 Reasons for Choosing Combination of PEG6000 and Croscarmellose Sodium

Firstly, PEG6000 has well an aqueous solubility and miscible with most of the organic solvent. In addition, its melting point is in 55-65°C range (Kumari, Chandel, & Kapoor, 2013) and has no incompatibility with croscarmellose sodium (Rowe, Sheskey, & Quinn, 2009). Furthermore, the polymer is inexpensive and available.

Secondly, croscarmellose sodium is a super disintegrant. It facilitates the water uptake through promoting liquid penetration, using capillary forces to suck water into the pores of granules or tablets (Aulton, 2007). Moreover, it does not show any incompatibility with PEG6000 in normal condition (Rowe, Sheskey, & Quinn, 2009). Croscarmellose sodium is also inexpensive and available.

1.16 Fenofibrate

1.16.1 Description

Fenofibrate, isopropyl ester of 2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl propanoic acid, is hydrophobic in nature and has molecular weight of 360.84. Fenofibrate is white or almost white, crystalline powder. It is practically insoluble in water, slightly soluble in alcohol and very soluble in methylene chloride (BP, 2005). Its melting point is 79-82°C.

1.16.2 Clinical Pharmacology

Fenofibrate is a lipid lowering drug and fall under fibrates group of hypolipidaemic drugs. Fibrates are isobutyric acid derivatives. Fenofibrate is a second generation prodrug fibric acid derivatives. They primarily activate lipoprotein lipase (a key enzyme in the degradation of VLDL). Consequently, it lowers the circulating TGs. Lipoprotein lipase production and fatty acid oxidation increase through the activation of PPAR- α (a gene transcription regulating the expression of receptor in liver, fat and muscles). In addition second generation fibrates like fenofibrates also mediate enhanced LDL receptor expression in liver (Singh, Baghel, & Yadav, 2011).

Fenofibrate is most effective in type III, IV and V hyperlipoproteinaemia. The drug may use as an adjuvant drug in type IIb patients. The reported adverse effects are myalgia and hepatitis rashes (Tripathi, 2008).

1.16.3 Fenofibrate as an Ideal Candidate for Solid Dispersion

Fenofibrate is an ideal candidate for solid dispersion as it is in BCS class II drug that have low aqueous solubility and high permeability. Hence, bioavailability is a rate limiting step for the absorption of drug from the gastrointestinal tract. The drug is practically insoluble in water where it has higher lipophilicity ($\log P = 5.24$). Recently this drug is marketed in 85 countries and available mostly in micronized form (Singh, Baghel, & Yadav, 2011).

1.17 Literature Review

Dissolution enhancement work on Fenofibrate using the combination of croscarmellose sodium and PEG6000 has not been done yet. Very few works have been done with PEG6000 using physical mixture method and solvent method with ethanol.

In research work of “Study on the effect of different polymers on in-vitro dissolution profile of Fenofibrate by solid dispersion technique” in “Journal of Applied Pharmaceutical Science” the solid dispersion with PEG6000 was carried out using solvent method. The formulation containing 1200mg PEG6000 has showed greater dissolution 100.61% within 60 minutes of dissolution (Saffoon, Uddin, Huda, & Bishwajit, 2011).

In “Solubility enhancement and solid state characterization of Fenofibrate solid dispersions with polyethylene glycol 6000 and 8000” in “Journal of Pharmacy Research” physical method and melting method were carried out at drug and PEG6000 ratio 1:1, 1:2, 1:3 and 1:5. It has been found out that the dissolution performance increases with increasing amount of PEG6000 (Bonthagarala, Nama, Nuthakki, Kiran, & Pasumsrthi, 2014).

Chapter 2:

Methodology

2.1 List of Instruments, Apparatus and Glass Wares

Table 2.1: List of instruments and equipment used in the analysis

Serial Number	Instrument	Model/Manufacturer	Country of Origin
1	Electronic balance	Shimadzu	Japan
2	Dissolution Tester	Logan Instruments Corp., UDT-804	USA
3	UV-Visible Spectrophotometer	Hitachi	Japan
4	Water suction filtration	Shimadzu	Bangladesh

Table 2.2: List of apparatus and glass wares used in the experiment

Serial Number	Name	Specification
1	Volumetric flask	10ml
2	Pipette(graduated & volumetric)	1ml,10ml
3	Beakers	10ml,50ml,100ml
4	Measuring cylinder	100ml,1000ml
5	Pipette filler	Bangladesh
6	Mortar & Pestle	Small

2.2 Preparation of 0.72% sodium lauryl sulphate

7.2g of sodium lauryl sulphate was dissolved in 1000ml of distilled water to produce 1litre 0.72% dissolution media.

2.3 Preparation of Solid Dispersion by Solvent Method

200mg of seven times Fenofibrate were correctly weighed and were kept in seven 10ml beakers separately. 8ml of ethanol was added in each formulation (F4, F5, F6, F8, F9, F10 and F11). Drug was completely dissolved in the solvent. Different ratios of PEG6000 and croscarmellose sodium were added in the solution at specific amount according to formulations. Then they were sonicated for five minutes. All solutions were kept at normal environment for one day. When the solutions were evaporated completely, they were crushed in mortar and pestle.

2.4 Preparation of Physical Mixture Method

Physical mixture of Fenofibrate with different combination of PEG6000 and croscarmellose sodium of from F1 to F13 was prepared separately. In each formulation Fenofibrate and the combine form of PEG6000 and croscarmellose sodium at specific amount according to the formulation were accurately weighed, pulverized and then mixed thoroughly by light tituration for five minutes in small mortar and pestle for each formulation until homogenous mixture was obtained.

2.5 List of Formulation Code with their Compositions and Respective Method

Table 2.3 is showing the composition of each formulation both in physical mixture method and solvent evaporation method. Here the pure drug ratio is always same for each formulation. Only thing differ is the different ratio of combination of PEG6000 and croscarmellose sodium.

Table 2.3: Name of Methods, Compositions & code of Formulation, Ratio of drug and excipients

Name of Methods	Compositions	Drug: Polymer: Disintegrate Ratio(mg)	Formulation Code
Physical Mixture	Fenofibrate (200mg)	–	PD
	Fenofibrate: PEG6000: Croscarmellose Sodium	200:2:5	F1
		200:5:10	F2
		200:10:20	F3
		200:15:30	F4
		200:20:40	F5
		200:30:60	F6
		200:80:160	F7
		200:40:20	F8
		200:50:25	F9
		200:60:30	F10
		200:70:35	F11
		200:80:40	F12
		200:160:80	F13
Solvent Method	Fenofibrate: PEG6000: Croscarmellose Sodium	200:15:30	F4
		200:20:40	F5
		200:30:60	F6
		200:40:20	F8
		200:50:25	F9
		200:60:30	F10
		200:70:35	F11

2.6 Pictures & Images of the Instruments



Figure 2.1: Picture showing an electronic balance



Figure 2.2: Picture showing UV-Visible spectrophotometer



Figure 2.3: Picture showing dissolution tester

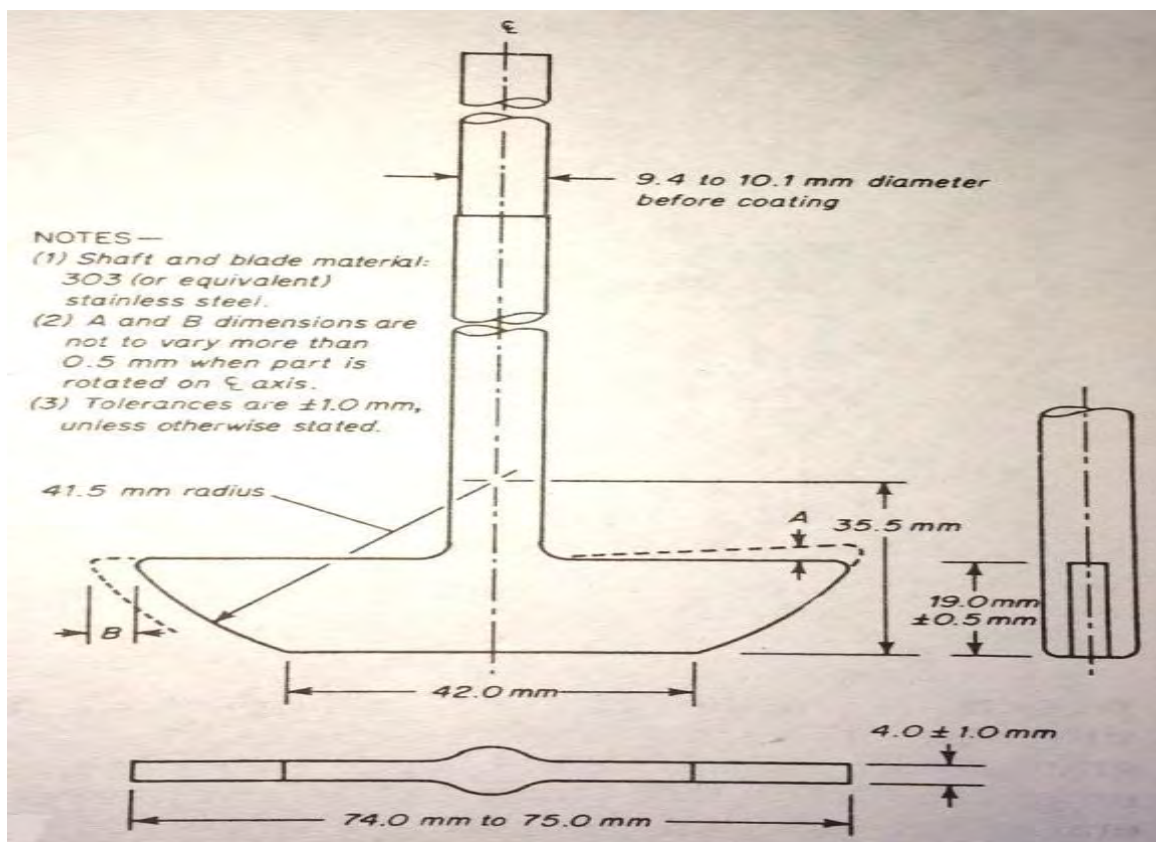


Figure 2.4: Picture showing the paddle of dissolution tester

2.7 In vitro Dissolution Study

2.7.1 Principle

Release rate of fenofibrate solid dispersions are carried on according to the general procedure of United States Pharmacopoeia (USP). Samples of dissolution fluid are withdrawn and analyzed by UV Spectrophotometer. The measurement is done at the wavelength at which the absorption is maximum. By comparing with absorbance of standard solution, the amount of active fenofibrate in solid dispersions released is calculated.

2.7.2 Conditions

Table 2.4: Conditions in dissolution testing

Apparatus	USP 2 Paddle
Dissolution medium	0.72% Sodium lauryl sulfate in distilled water, 1000mL, deaerated.
Temperature	36.7°C (±0.5)
Stirring Speed	75rpm
Time	30 inutes

2.7.3 Preparation of Standard Solution

10mg of working standard of Fenofibrate was weighed and transferred into a clean and dry 10ml volumetric flask. Then 10ml of methanol was added to the volumetric flask and shaken properly to get concentration about 1000µg/ml. 2ml of above stock solution was diluted to 10ml with methanol in another 10ml volumetric flask to get a secondary stock solution of 200µg/ml. From this stock solution series of dilutions with concentration of 5, 10, 15, 20, 25, 30µg/ml in methanol were prepared in separate volumetric flasks.

2.7.3 Standard Curve of Fenofibrate

Table 2.5: Standard Curve of Fenofibrate

Concentration (µg/ml)	Absorbance
5	0.1
10	0.21
15	0.32
20	0.434
25	0.54
30	0.62

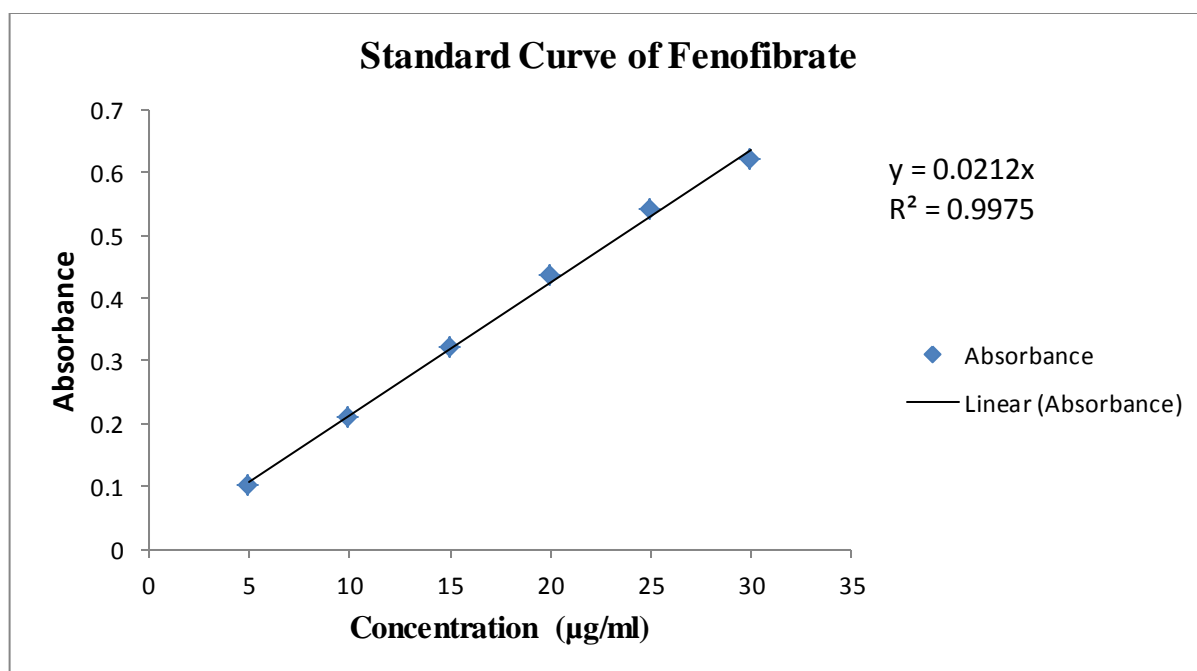


Figure 2.5: Standard curve of Fenofibrate

2.7.1 Preparation of Sample Solutions

1000ml of dissolution media was placed into each of six dissolution vessels and the temperature was set to 37⁰C (±0.5). Solid dispersion formulations were transferred to each six baskets. The baskets were immersed into the medium to a distance 25±2 mm between the basket and bottom of the vessel. The apparatus was started to operate at the specified rpm. At the end of 30min, 10ml samples were withdrawn from each vessel. 1ml sample from that withdrawn sample was taken in a 10ml volumetric flask and 9ml media was added to it. This was done for every withdrawn sample to get a concentration of 20µg/ml.

Then the absorbance of the above solution in a 1cm silica cell were measured at the wavelength of maximum absorbance at 290nm(according to USP) by UV-visible spectrophotometer using media as blank. The percentage of drug release from the solid dispersion formulations were calculated with the help of straight-line equation obtained from the standard curve of Fenofibrate. The dissolution was continued for 30 minute in the in-vitro condition.

2.8 Collection of Samples

The source of Fenofibrate was Nexchem pharmaceutical company, china. PEG 6000 and Croscarmellose sodium were obtained pharmaceutical technology laboratory in Pharmacy department of BRAC University. All other reagents and solvent used were of analytical grade.

Chapter 3:

Result and Discussion

3.1 In Vitro Dissolution Study Results

Table 3.1: Table showing percentage of drug release in physical method from F1 to F7

Physical Mixture	
Formulation Code	% of Drug Release
PD	8.9
F1	10.5
F2	29
F3	29.5
F4	31
F5	32.5
F6	22
F7	22.5

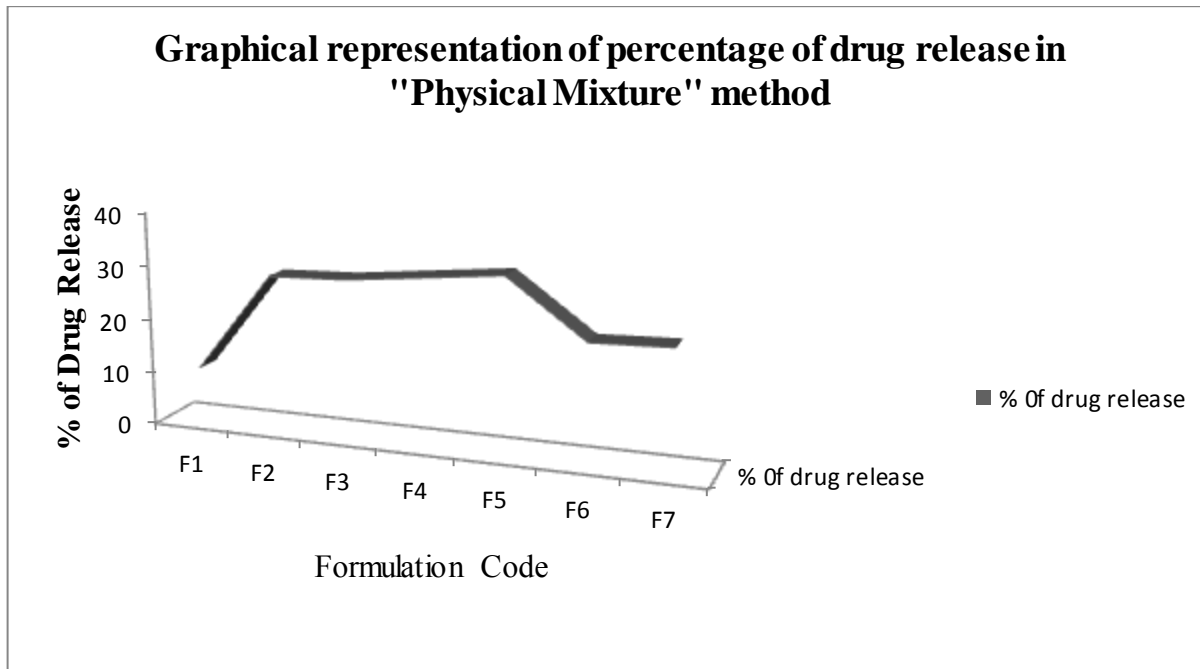


Figure 3.1: The line showing the increase and decrease of the percentage of drug release in physical Mixture from F1 to F7

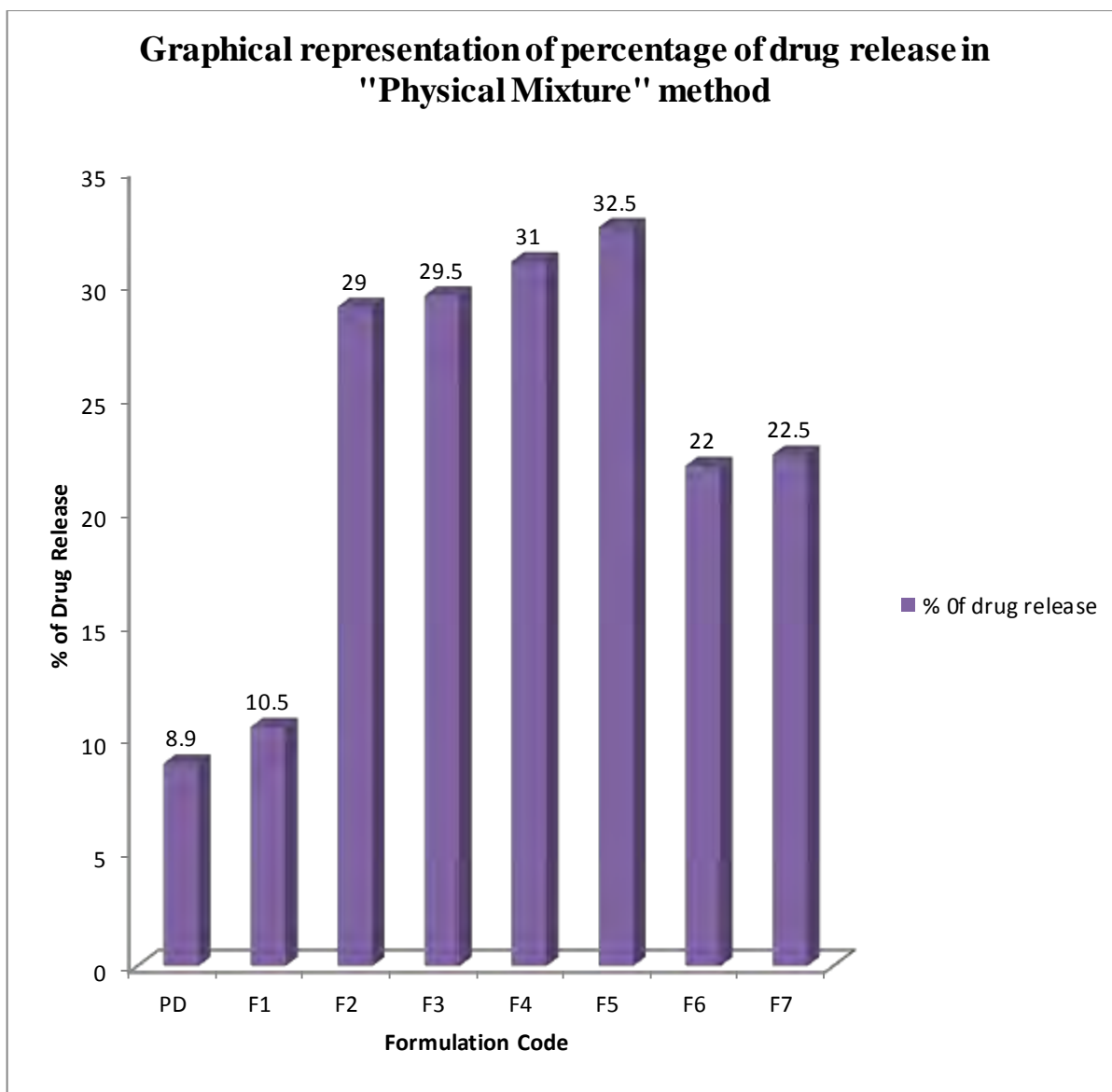


Figure 3.2: Bar chart showing the percentage of drug release in physical mixture from F1 to F7

Table 3.2: Table showing percentage of drug release in physical mixture from F8 to F13

Physical Mixture	
Formulation Code	% of Drug release
PD	8.9
F8	40
F9	42.5
F10	47.5
F11	83
F12	35
F13	25.5

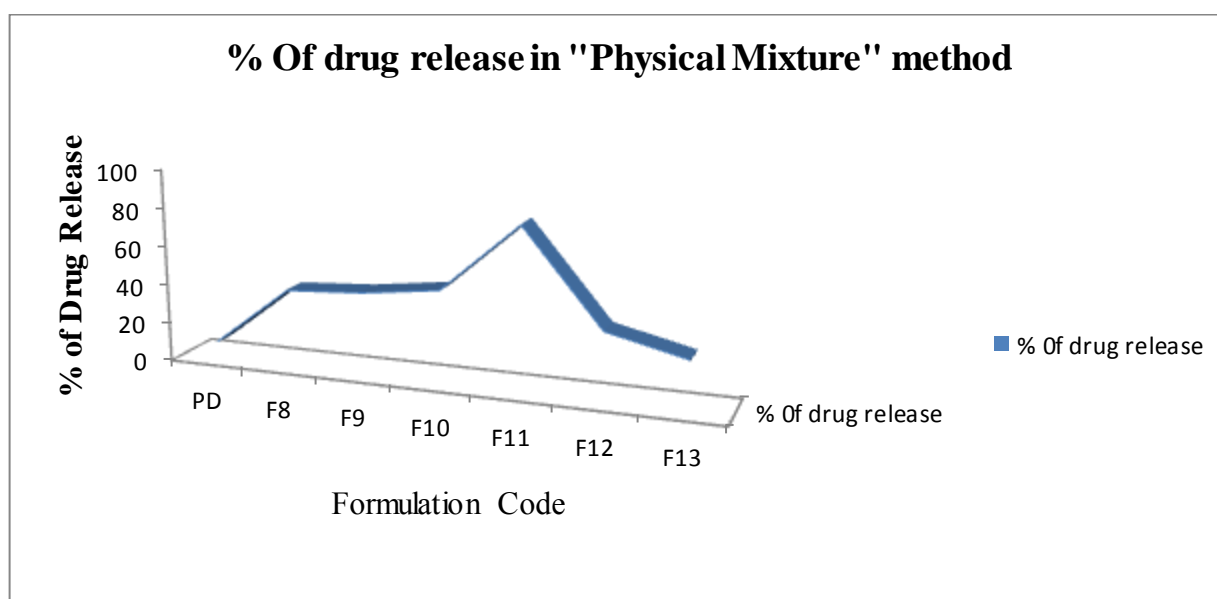


Figure 3.3: The line showing the increase and decrease of the percentage of drug release in physical mixture from F8 to F13

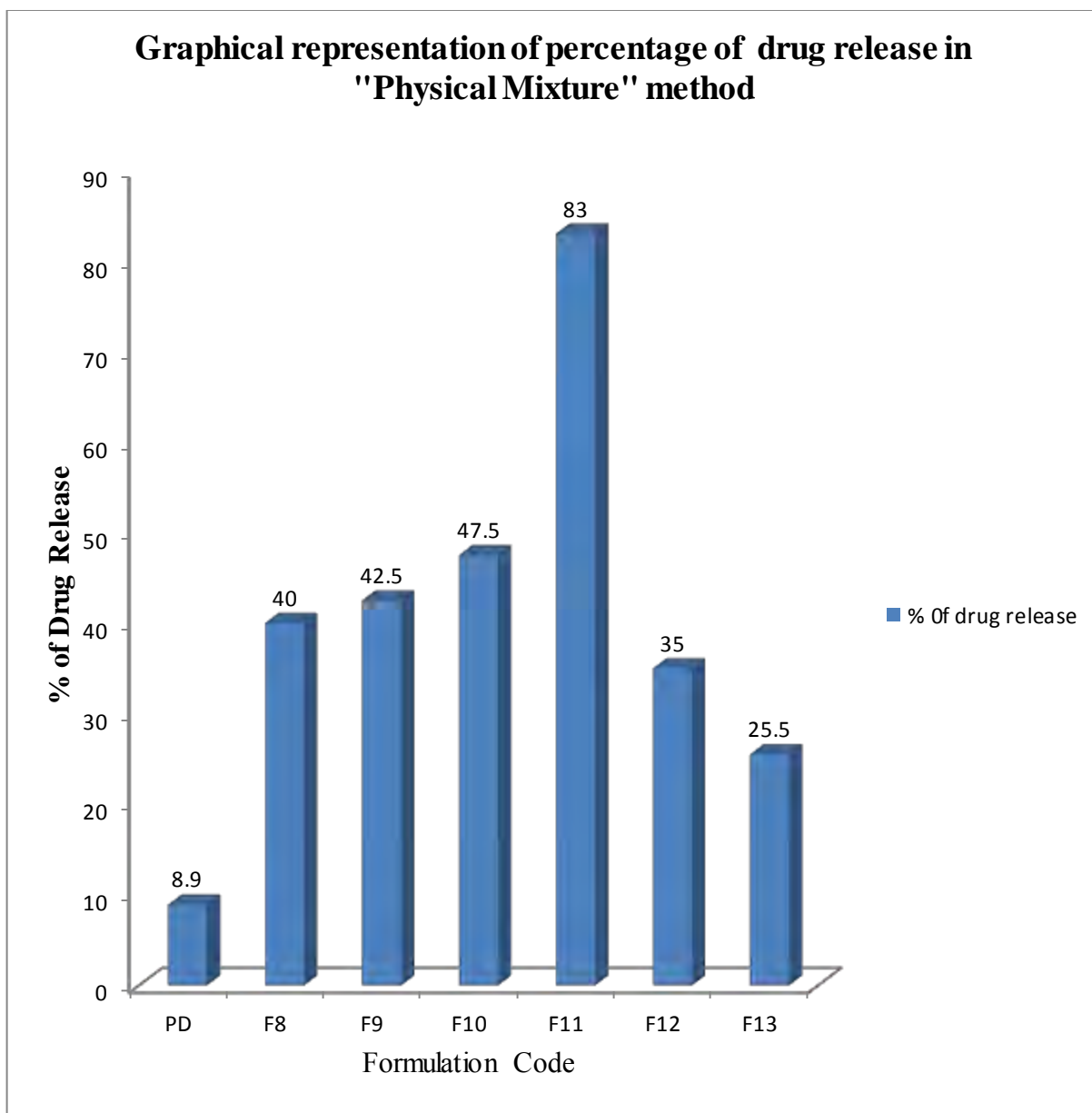


Figure 3.4: Bar chart showing the percentage of drug release in physical mixture from F8 to F13

Table 3.3: Table showing percentage of drug release in Solvent method from F4 to F6

Solvent Method	
Formulation Code	% of Drug Release
PD	8.9
F4	30.5
F5	32.5
F6	39

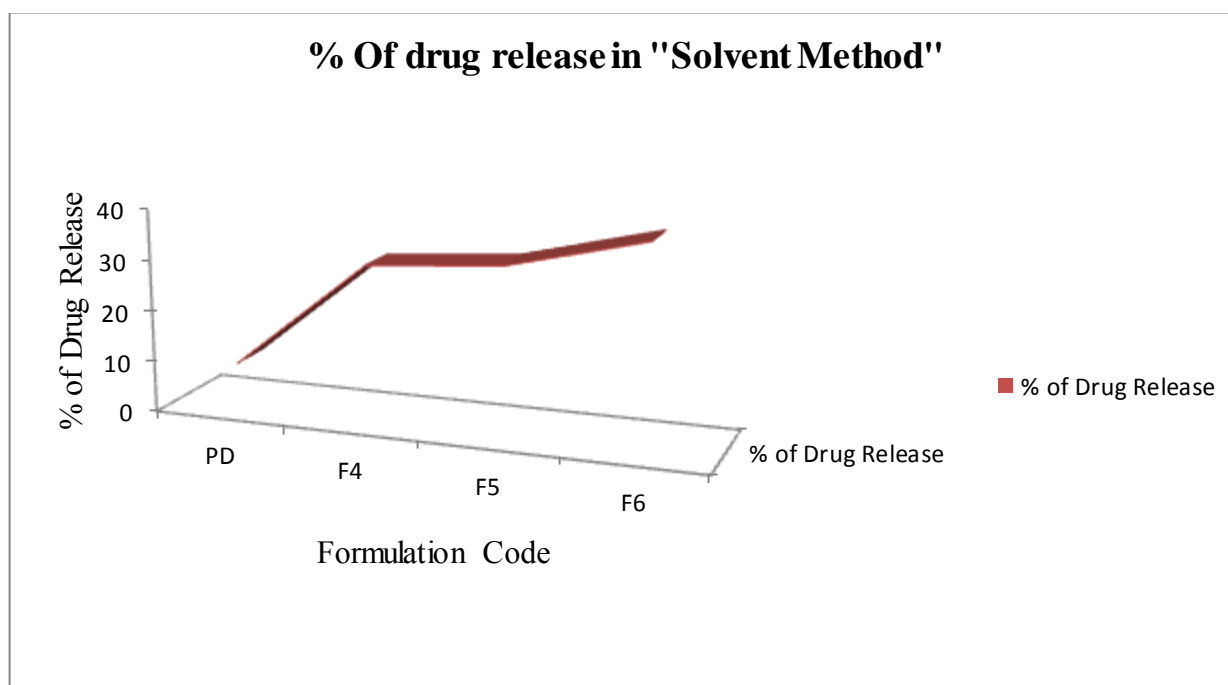


Figure 3.5: The line showing the increase and decrease of the percentage of drug release in Solvent method from F4 to F6

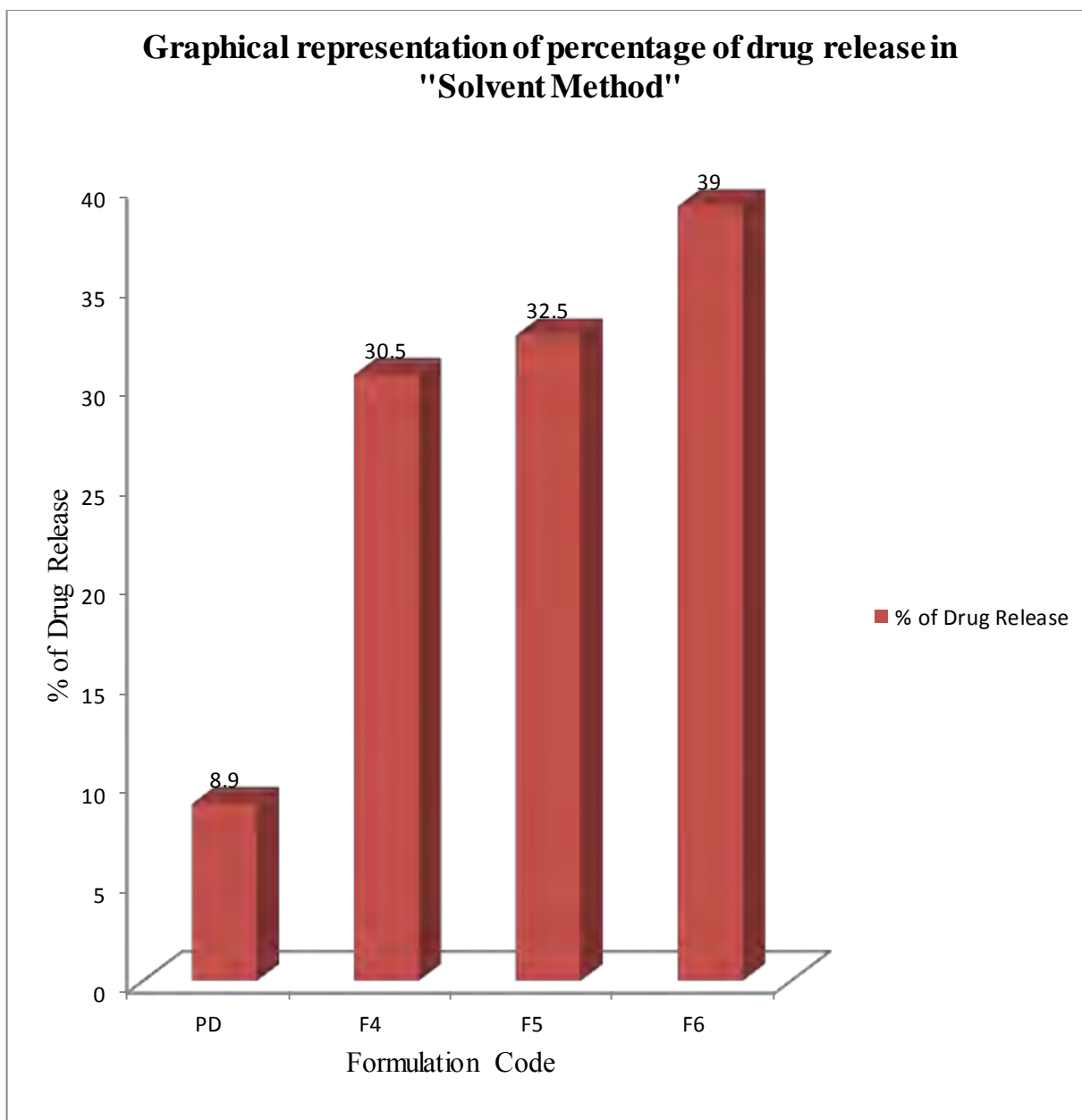


Figure 3.6: Bar chart showing the percentage of drug release in Solvent Method from F4 to F6

Table 3.4: Table showing percentage of drug release in Solvent method from F8 to F11

Solvent Method	
Formulation Code	% of Drug Release
PD	8.9
F8	24
F9	28
F10	33
F11	38.5

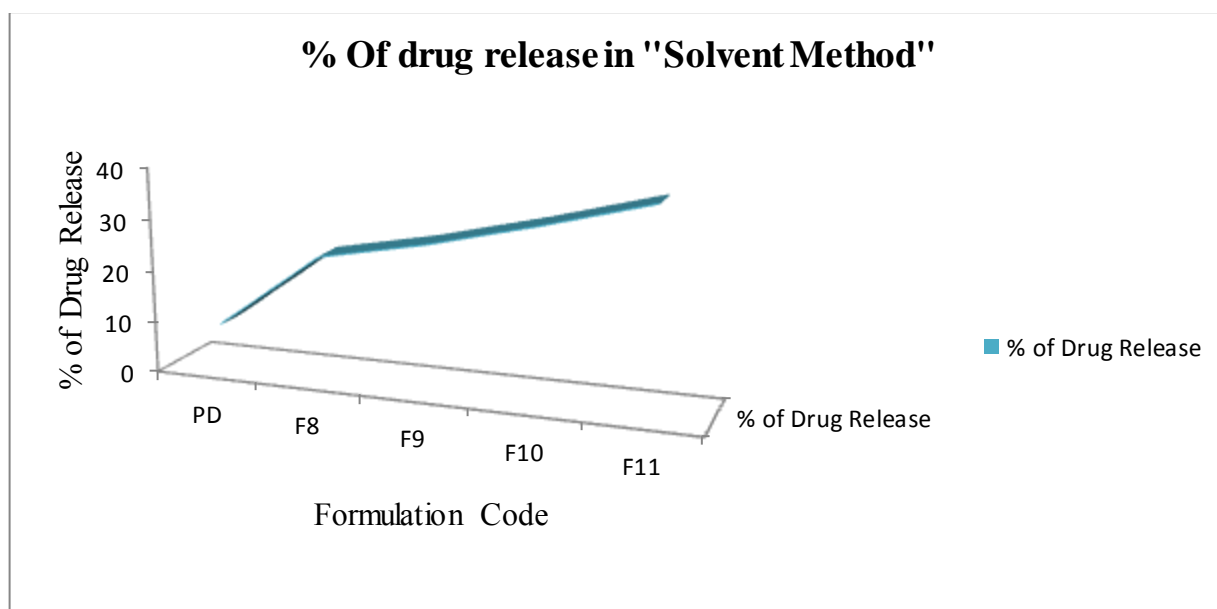


Figure 3.7: The line showing the increase and decrease of the percentage of drug release in Solvent method from F8 to F11

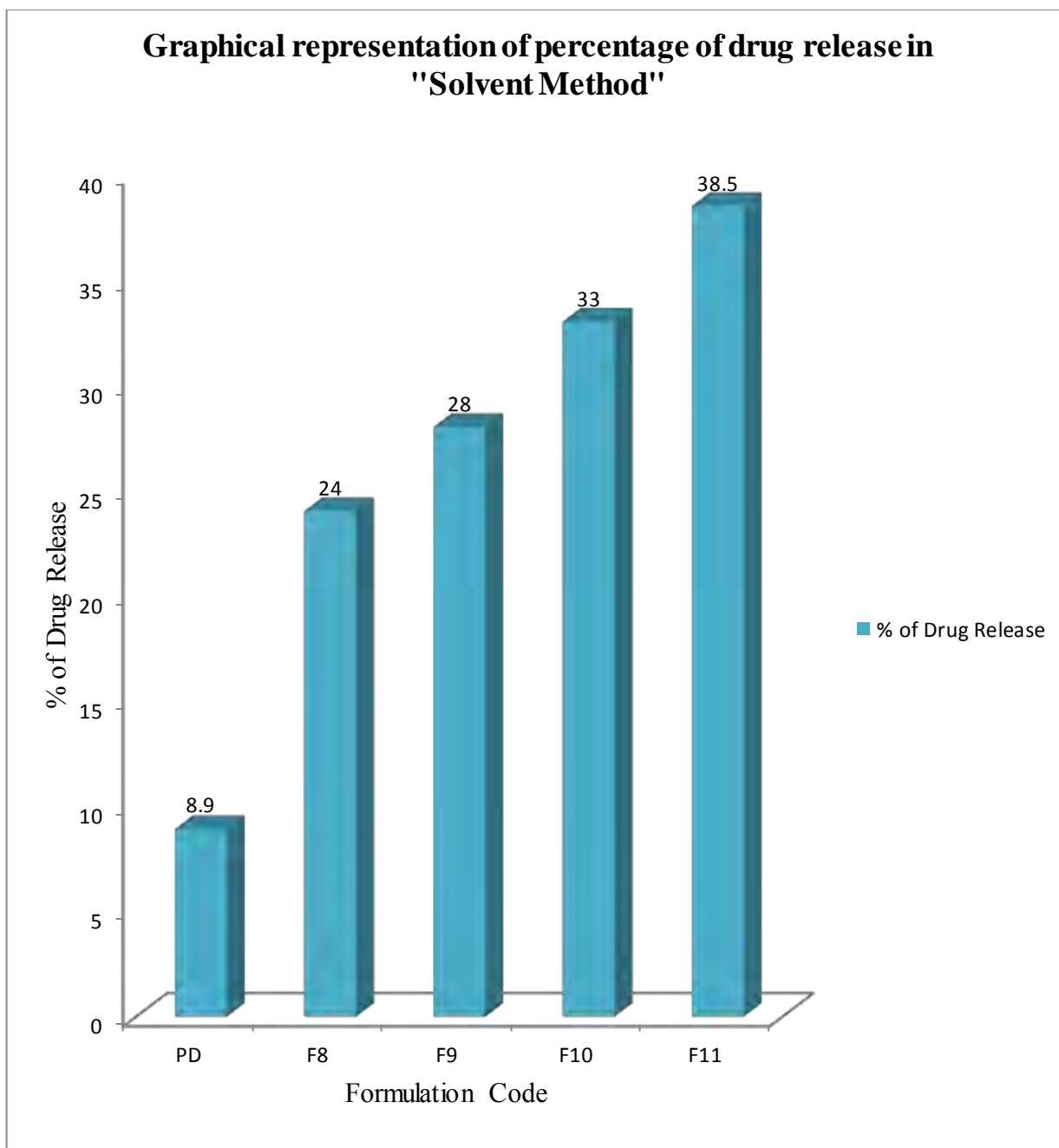


Figure 3.8: Bar chart showing the percentage of drug release in Solvent Method from F8 to F11

Table 3.5: Table showing Difference percentage of drug release in Solvent method and Physical Method from F4 to F6

Formulation Code	% of Drug Release in Solvent Method	% of Drug Release in Physical Mixture
F4	30.5	31
F5	32.5	32.5
F6	39	22

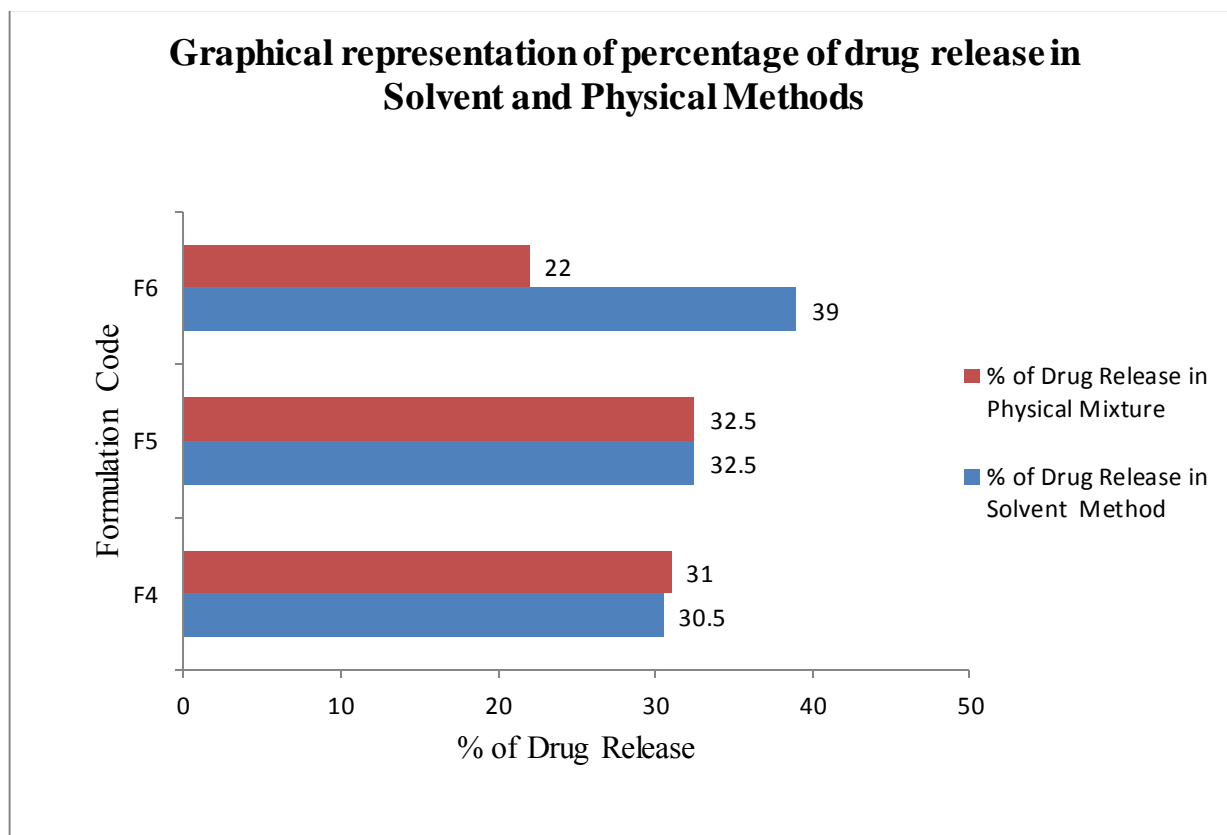


Figure 3.9: Bar Chart showing Difference in percentage of drug release Between Solvent method and Physical Method from F4 to F6

Table 3.6: Table showing Difference percentage of drug release in Solvent method and Physical Method from F8 to F11

Formulation Code	% of Drug Release in Solvent SD Method	% of Drug Release in Co-grinding SD Method
F8	24	40
F9	28	42.5
F10	33	47.5
F11	38.5	83

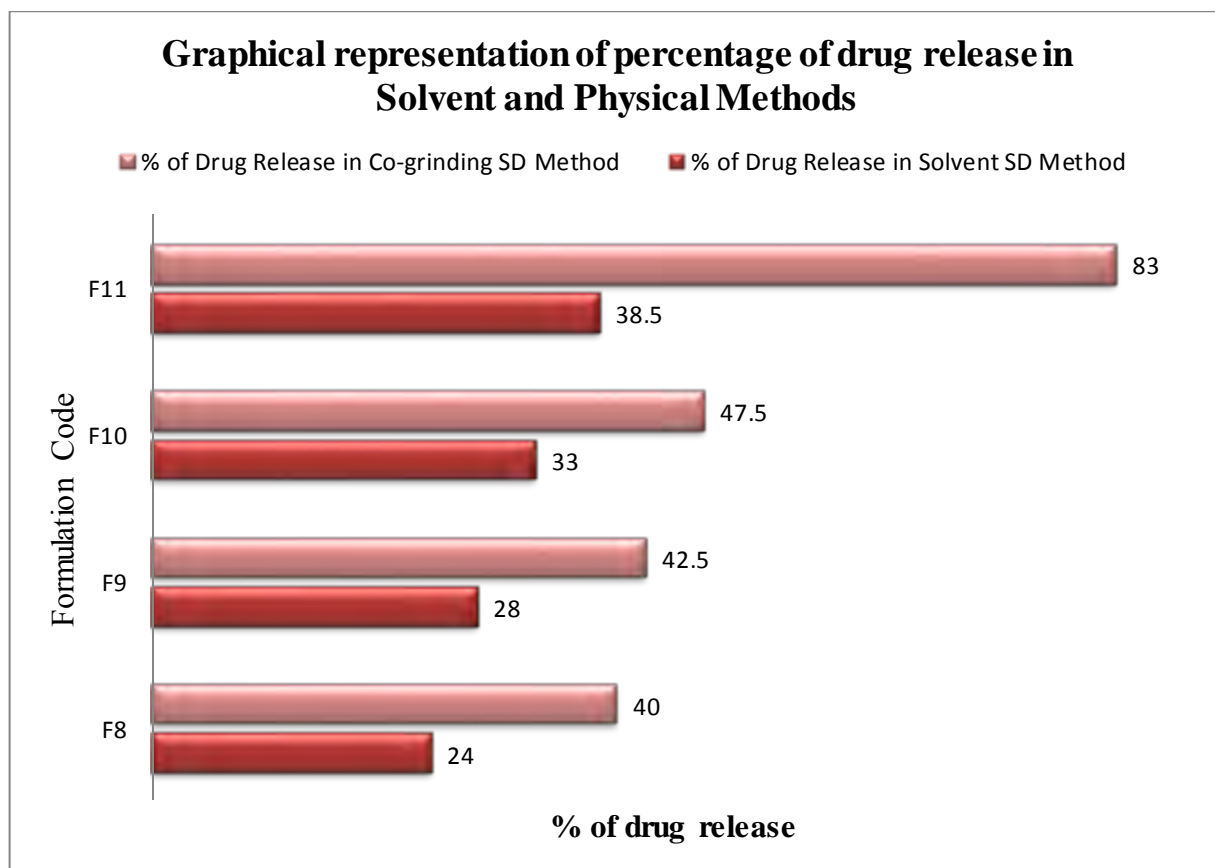


Figure 3.10: Bar Chart showing Difference in percentage of drug release Between Solvent method And Physical Method from F8 to F11

3.2 Discussion

The prime aim of this project is to overcome the solubility problems of Fenofibrate through two easy and inexpensive methods in solid dispersion named physical mixture method and solvent evaporation method. Different formulations with different ratio of polymer and disintegrant mixture were designed. Percentages of drug release of each formulation were calculated from the slope of the appropriate plot and regression coefficient (r^2) was determined.

Table 3.1 is showing the percentage of drug release in physical mixture method of solid dispersion from F1 to F7 within 30 minutes. All the formulations showed a small extent of dissolution improvement from the plain drug. Among these formulations F5 showed higher percentage of drug release than other and it was 32.5%. It was seen that from F1 to F5 the percentage of drug release were increasing but from F6 to F7 the percentage of drug release has fallen to some extent. So it can be said, in the ratio between PEG6000 and croscarmellose sodium with drug, if the amount of croscarmellose sodium is higher than the PEG6000 then the percentage of drug release increases. However, from 30:60 ratio of PEG6000 and croscarmellose sodium with same amount of drug, the percentage of drug release has fallen. It can be concluded that up to 20:40 ratio the percentage of drug release increase in physical mixture method but from 30:60 the percentage of drug release falls. As a hydrophilic polymer PEG6000 offers usually better surface area for the hydrophobic Fenofibrate drug and croscarmellose sodium as a super disintegrants break up granules into primary powder particles in order to increase surface area and in addition to facilitate water uptake. Still high swelling disintegrant like sodium croscarmellose should be given in low concentration in the formulation or up to (1-5) % (Aulton, 2007). Otherwise the high concentration of disintegrants make too much fine particles that aggregates and produces lump instead of deaggregation and affects the dissolution and oral bioavailability. In result, with high concentration of croscarmellose sodium the percentage of drug release falls. In figure (3.1 and 3.2) up and downing of the percentage of drug release from F1 to F7 has shown.

Next, table 3.2 is showing the percentage of drug release in physical mixture method of solid dispersion from F8 to F13 within 30 minutes. All the formulations showed a small extent of dissolution improvement from the plain drug. Among these formulations F11 showed higher

percentage of drug release than all F1 to F13 and it was 83%. It was seen that from F8 to F11 the percentage of drug release were increasing but from F12 to F13 the percentage of drug release has fallen to some extent. So it can be said, in the ratio between PEG6000 and croscarmellose sodium with drug, if the amount of the PEG6000 is higher than croscarmellose sodium then the percentage of drug release increases. However, from 80:40 ratio of PEG6000 and croscarmellose sodium with same amount of drug, the percentage of drug release has fallen. It can be concluded that below 80:40 ratio the percentage of drug release increase in physical mixture method but from 80:40 the percentage of drug release falls. The falling of percentage of drug may be due to the higher concentration of both polymer and disintegrant that form lumps and interact drug release from its dosage form. In figure (3.3 and 3.4) up and downing of the percentage of drug release from F8 to F13 has shown.

Several mechanisms may be possible to the enhanced release of Fenofibrate in the physical mixture method in solid dispersion. The faster dissolution of the drug from the solid dispersions is attributed to the enhancement of wettability as hydrophilic carrier PEG6000 and disintegrant croscarmellose sodium are used and decrease in the aggregation of the hydrophobic drug particles.

Table 3.3 is showing the percentage of drug release in solvent evaporation method of solid dispersion from F4 to F6 within 30minutes. All the formulations showed a small extent of dissolution improvement from the plain drug. Among these formulations F6 showed higher percentage of drug release than other and it was 39%. It was seen that from F4 to F6 the percentage of drug release were increasing. So it can be said, in the ratio between PEG6000 and croscarmellose sodium with drug and solvent, if the amount of croscarmellose sodium is higher than the PEG6000 then the percentage of drug release increases. In figure (3.5 and 3.6) the gradual increasing of the percentage of drug release from F4 to F6 has shown.

Table 3.4 is showing the percentage of drug release in solvent evaporation method of solid dispersion from F8 to F11 within 30minutes. All the formulations showed a small extent of dissolution improvement from the plain drug. Among these formulations F11 showed higher percentage of drug release than other and it was 38.5%. It was seen that from F8 to F11 the percentage of drug release were increasing. So it can be said, in the ratio between PEG6000 and croscarmellose sodium with drug and solvent, if the amount of the PEG6000 is higher

than croscarmellose sodium then the percentage of drug release increases. In figure (3.7 and 3.8) the gradual increasing of the percentage of drug release from F8 to F11 has shown.

Increased dissolution of Fenofibrate in solvent evaporation method of solid dispersion could be probable reduction in its particle size, wetting of the hydrophobic particles and amplification of its solubility by PEG6000 and croscarmellose sodium. Furthermore, due to the uniform distribution when this system comes in contact with an aqueous dissolution medium, the hydrophilic carrier dissolves and results in fine particles drugs with increased surface area. Moreover, other factors can be absence of aggregation or crystal growth of drug during dissolution.

Between physical mixture and solvent evaporation method, physical mixture method showed better result than solvent method in F4, F5, F6, F8, F9, F10, and F11. The comparison is shown in table (3.5 and 3.6) and figure (3.9 and 3.10). This is because drug, polymer and disintegrant have any incompatibility with ethanol and it lowers the percentage of drug release from the physical mixture in case whether the amount of disintegrant increases or PEG6000 increases.

In conclusion it can be said that, though in both methods of the solid dispersion the percentage of drug release within 30minutes have increased to some extent but only F11(83%) prepared in physical mixture method meet the specifications as the percentage of Fenofibrate release within 30minutes should be 80% according to USP.

Chapter 4:

Conclusion

4.1 Conclusion

Physical mixture method and solvent method are two simple and effective methods in solid dispersion for increase dissolution performance and solubility. The present study was carried out to investigate the utility of the combination of PEG6000 and croscarmellose sodium in physical mixture method and solvent method. All the preparations in both physical mixture method and solvent method have showed better drug dissolution than that of plain drug within 30minutes. It can be assume that both techniques increase the solubility of the Fenofibrate in aqueous medium. Therefore, the percentage of drug release showed better dissolution within 30 minutes. For further investigation with the combination of PEG6000 and croscarmellose sodium and Fenofibrate, this work can help in many ways.

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